NOTE Communicated by Charles Stevens

Cortical Cells Should Fire Regularly, But Do Not

William R. Softky
Christof Koch
Computation and Neural Systems Program,
California Institute of Technology, Pasadena, CA 91125 USA

When a typical nerve cell is injected with enough current, it fires a regular stream of action potentials. But cortical cells *in vivo* usually fire irregularly, reflecting synaptic input from presynaptic cells as well as intrinsic biophysical properties. We have applied the theory of stochastic processes to spike trains recorded from cortical neurons (Tuckwell 1989) and find a fundamental contradiction between the large interspike variability observed and the much lower values predicted by well-accepted biophysical models of single cells.

Over 10,000 extracellular spike trains were recorded from cells in cortex of the awake macaque monkey responding to various visual stimuli. These trains were recorded from V1 (Knierim and Van Essen 1992) and MT (Newsome *et al.* 1989). Traces were chosen from well-isolated, fast-firing, nonbursting neurons. Because the firing frequency varied over the course of the stimulus presentation, each interspike interval Δt (i.s.i.) was assigned to 1 of 10 histograms for that cell, with each histogram representing a narrow range of instantaneous firing rates, for example, 50–100 Hz, 250–300 Hz.

From each histogram we computed a measure of the variability of the spike train, the dimensionless coefficient of variation (CV), which is the ratio of the standard deviation to the mean of the i.s.i. histogram:

$$CV = \sigma_{\Delta t}/\overline{\Delta t} \tag{0.1}$$

The approximate CV values measured here are in good agreement with other reports of CV (Douglas and Martin 1991; Burns and Webb 1976): interspike intervals are near-random, and close to that expected for the i.s.i. histogram of a pure Poisson process (i.e., $CV \approx 0.5$–1; see Fig. 1).

We attempted to account for this observed variability using a simple integrate-and-fire model requiring N random (Poisson) impulse inputs to reach the threshold (Tuckwell 1989). For such a neuron, $CV = 1/\sqrt{N}$. An absolute refractory period t_0 reduces this value when $\overline{\Delta t}$ is near t_0

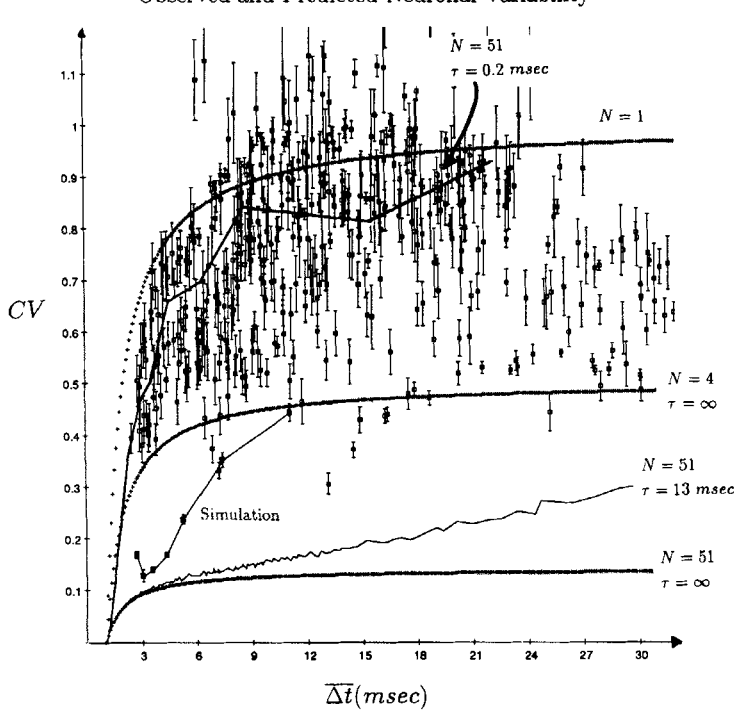

Figure 1: Comparison of the randomness measure CV as a function of interspike interval $\overline{\Delta t}$ for three different data sets: (1) experimentally recorded, nonbursting, macaque cortical neurons (MT and V1; empty squares; we observed no systematic difference between the two data sets); (2) detailed compartmental simulation of a reconstructed layer **V** pyramidal cell (filled, connected squares); (3) different integrate-and-fire models with refractory period of 1.0 msec and N EPSPs required to fire (crosses and jagged lines). Crosses are predictions by integrate-and-fire models with $N = 1$ (top), $N = 4$ (middle), and $N = 51$ (bottom). Jagged lines show simulated leaky integrators with $N = 51$: $\tau_m = 0.2$ msec (top) or $\tau_m = 13$ msec (bottom). Conventional parameters (i.e., $\tau_m > 10$ msec and $N > 50$) fail to account for the high variability observed.

(Tuckwell 1989). Numerical simulations with a leak term $\tau_m = RC$ show that CV increases significantly only for $\overline{\Delta t} \gg \tau_m$. CV can also increase during periods of very strong inhibition, but such inhibition was not found in a recent electrophysiological search (Berman *et al.* 1991). Because most researchers estimate that 100 or more inputs are required to trigger a cell (Douglas and Martin 1991; Abeles 1991), as well as $\tau_m \geq 10$ msec and

$t_0 \geq 1.0$ msec, the above models predict that CV should be far lower than is seen in the monkey data for the high firing rates observed (see Fig. 1).

There remains the possibility that more realistic Hodgkin–Huxley neurons (whose firing currents are continuous functions of voltage) might be able to amplify input irregularities more effectively than the highly simplified integrate-and-fire neuron above, which has a discontinuous firing threshold and no such sensitive voltage regime. We expect that this difference would be significant only in a neuron whose soma spends most of its "integration time" resting just below threshold (unlike the cortical cells in question, which have high firing rates and hence no stationary resting potential during periods of peak activation). But the only persuasive test would be the simulation of a Hodgkin–Huxley-like neuron in the presence of random synaptic input.

We therefore simulated a biophysically very detailed compartmental model of an anatomically reconstructed and physiologically characterized layer **V** pyramidal cell (Bernander *et al.* 1991). The model included not only the traditional Hodgkin–Huxley currents, but five additional active currents at the cell body (I_{Na}, I_{Na-p}, I_{Ca}, I_{DR}, I_A, I_M, $I_{K(Ca)}$), 820 compartments, and a passive decay time of $\tau_m = 13$ msec. Spatially distributed random (Poisson) excitatory synaptic conductance inputs gave rise to strong somatic EPSPs with mean amplitudes around 1.6 mV.

We provided enough synaptic input to this cell to generate 200 spike trains (with mean frequencies comparable to the spike trains recorded from monkey) and subjected them to the same analysis. The resulting CV values agree with the simple integrator models, and disagree strongly with the monkey data (see Fig. 1). In addition, the number of spikes n in each simulated train varied by no more than a few percent, a much smaller amount than the $\sqrt{n}$ variation observed for real cells. Therefore, we conclude that the present knowledge of pyramidal cell biophysics and dynamics is unable to account for the high CV seen in fast-firing monkey visual cortex neurons: these cells should fire regularly, but do not.

Neither the data nor the model used here are controversial. But they are not consistent with each other. Only a few situations could cause near-random, fast firing in these monkey cells: for example, strong synaptic conductance changes that create a very fast effective time constant ($\tau_m \leq 0.2$ msec; see Fig. 1), or nonrandom synaptic input, which is highly synchronized on a millisecond scale (Abeles 1991; Koch and Schuster 1992). In the absence of such phenomena, the Central Limit Theorem makes these cells observed near-random spiking inconsistent with their assumed role as devices that temporally integrate over many inputs. Thus, it may well be that the time scale of cortical computation is much faster than previously realized.

Acknowledgments

This research was funded by a NSF Presidential Young Investigator Award, by the Office of Naval Research, and by the James S. McDonnell Foundation.

References

Abeles, M. 1991. *Corticonics.* Cambridge University Press, New York.

Berman, N., Douglas, R., Martin, K., and Whitteridge, D. 1991. Mechanisms of inhibition in cat visual cortex. *J. Physiol.* **440**, 697–722.

Bernander, Ö., Douglas, R., Martin, K., and Koch, C. 1991. Synaptic background activity determines spatio-temporal integration in single pyramidal cells. *Proc. Natl. Acad. Sci. U.S.A.* **88**, 11569–11573.

Burns, B., and Webb, A. C. 1976. The spontaneous activity of neurones in the cat's cerebral cortex. *Proc. R. Soc. London B* **194**, 211–223.

Douglas, R., and Martin, K. 1991. Opening the grey box. *Trends Neurosci.* **14**, 286–293.

Knierim, J., and Van Essen, D. 1992. Neuronal responses to static textural patterns in area V1 of the alert macaque monkey. *J. Neurophysiol.* **67**, 961–980.

Koch, C., and Schuster, H. 1992. A simple network showing burst synchronization without frequency locking. *Neural Comp.* **4**, 211–223.

Newsome, W., Britten, K., Movshon, J. A., and Shadlen, M. 1989. Single neurons and the perception of motion. In *Neural Mechanisms of Visual Perception,* D. Man-Kit Lam and C. Gilbert, eds., pp. 171–198. Portfolio Publishing Co., The Woodlands, TX.

Tuckwell, H. C. 1989. *Stochastic processes in the neurosciences.* Society for Industrial and Applied Mathematics, Philadelphia.

Received 29 October 1991; accepted 4 February 1992.